Immune Globulins
Therapeutic Class Review (TCR)

August 17, 2016

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indications
Intravenous		
Bivigam®[1]	Biotest Pharmaceuticals Corporation	▪ Primary humoral immunodeficiency
Carimune NF, Nanofiltered®[2]	CSL Behring	▪ Primary humoral immunodeficiency ▪ Immune thrombocytopenic purpura
Flebogamma® DIF 5% and 10%[3,4]	Grifols	▪ Primary (inherited) immunodeficiency ▪ Chronic primary immune thrombocytopenia (10% only)
Gammagard® S/D[5]	Baxter	▪ Primary humoral immunodeficiency ▪ Prevention of bacterial infections in hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell chronic lymphocytic leukemia ▪ Chronic immune thrombocytopenic purpura ▪ Prevention of coronary artery aneurysms associated with Kawasaki syndrome
Gammaplex®[6]	Bio Products Laboratory	▪ Primary humoral immunodeficiency ▪ Chronic immune thrombocytopenic purpura
Octagam® 5% and 10%[7,8]	Octapharma USA	▪ Primary humoral immunodeficiency (5% only) ▪ Chronic immune thrombocytopenic purpura (10% only)
Privigen®[9]	CSL Behring AG	▪ Primary humoral immunodeficiency ▪ Chronic immune thrombocytopenic purpura
Intravenous or Subcutaneous		
Gammagard® Liquid[10]	Baxter	▪ Primary humoral immunodeficiency ▪ Multifocal motor neuropathy
Gammaked™[11]	Grifols Therapeutics (distributed by Kedrion Biopharm)*	▪ Primary humoral immunodeficiency ▪ Idiopathic thrombocytopenic purpura (IV use only) ▪ Chronic inflammatory demyelinating polyneuropathy (IV use only)
Gamunex®-C[12]	Grifols Therapeutics	▪ Primary humoral immunodeficiency ▪ Idiopathic thrombocytopenic purpura (IV use only) ▪ Chronic inflammatory demyelinating polyneuropathy (IV use only)
Subcutaneous		
Cuvitru™[13]	Baxalta	▪ Primary immune deficiency
Hizentra®[14]	CSL Behring AG	▪ Primary immune deficiency
immune globulin 10%/recombinant human hyaluronidase Hyqvia®[15]	Baxter	▪ Primary immune deficiency†

*Gammaked and Gamunex-C are manufactured by Grifols Therapeutics, and are identical; Kedrion Biopharma has an agreement with Grifols to market the product under a private label name (Gammaked).

†Safety and efficacy of chronic use of recombinant human hyaluronidase in Hyqvia have not been established in conditions other than primary immune deficiency.

OVERVIEW

Primary immunodeficiencies are inherited disorders of the immune system that predispose an individual to an increased rate and severity of infections as well as other possible sequelae such as autoimmune diseases and certain malignancies. Primary immune deficiencies are categorized as humoral (or antibody) deficiencies, cellular deficiencies, innate immune disorders, or a combination of deficiencies. The hallmark of humoral immunodeficiency is recurrent bacterial infections of the upper and lower respiratory tract.[16] Deficiency in the body's ability to fight infections through the humoral immune process predisposes an individual to significant morbidity and possible death from bacterial infections. Under normal circumstances, the body produces a variety of immunoglobulin (e.g., antibody) isotypes – Immune globulin A (IgA), Immune globulin G (IgG), and Immune globulin M (IgM). Deficiency of one isotype may be observed with deficiencies of the other isotypes. IgG deficiencies, in particular, increase an individual's susceptibility to a host of infections. Primary antibody deficiencies, which accounts for nearly 50% of the diseases categorized under the primary immunodeficiency disease (PIDD) umbrella, has been characterized based on the presence or absence of B cells as well as the quantity and quality of an individual's IgG pool.[17] B cells are integral to the body's humoral immune system by producing antibodies used to opsonize and neutralize foreign antigens, particularly bacterial and viral agents. If the B cell reservoir is impaired, the production of sufficient quantities of functional antibodies (Ab) is affected. Low numbers of immune globulin and/or antibodies of substandard quality require therapeutic intervention through the delivery of exogenous immune globulin preparations. Despite such varied phenotypic presentations, the continued hallmark of treatment for these diseases is the supplementation of immune globulin via either intravenous or subcutaneous means.

Table 1 outlines the various phenotypic categorizations of PIDD as offered by the American Academy of Allergy, Asthma, and Immunology (AAAAI).[18]

		IgG			
		Quantity/Quality			
		Absent/Absent	**Low/Low**	**Normal/Low**	**Low/Normal**
B cell	**Absent**	**Category I** ▪ Agamma-globulinemia ▪ SCID			
	Present		**Category II** ▪ Hyper IgM ▪ CVID ▪ NEMO deficiency	**Category III** ▪ Specific Ab Deficiency ▪ NEMO deficiency ▪ Subclass deficiency with specific antibody defect	**Category IV** ▪ Transient hypogamma-globulinemia of infancy ▪ Primary hypogamma-globulinemia

Table 1. Phenotypic categories of primary immunodeficiency disease. Adapted from Stiehm, et al. 2010.[19]

Ab = antibody, CVID = common variable immunodeficiency, NEMO = NF-kappa B Essential Modulator, SCID = severe combined immunodeficiency

In addition to its use in PIDD, exogenous immune globulin product has been FDA approved for use in certain neurologic disorders (multifocal motor neuropathy [MMN], chronic inflammatory demyelinating polyneuropathy [CIDP]) and other diseases (immune thrombocytopenic purpura [ITP], Kawasaki syndrome, B-cell chronic lymphocytic leukemia).[20]

Therapeutic immune globulin is prepared from pooled plasma obtained from between 15,000 and 60,000 healthy donors (1,000 to 10,000 Source Plasma units) at plasma donation centers in the United States.[21,22] The product provides exogenous immune globulin type G (IgG) antibodies. Pooling aids in offering broader coverage for a wide variety of antigens. Each FDA approved product is prepared using a slightly different isolation and purification method. A frequently used method involves a cold alcohol (ethanol) fractionation process which subjects the plasma lysate to a series of sequential purification steps to isolate the immune globulin from the various other plasma factors, such as Factor VIII and Factor IX.

Ig products are produced via such means that reduce the risk of viral exposure. Each product has validated their production methods to ensure the low risk of transmission of the viruses outlined in Table 2. The FDA issued guidance to assist manufacturers with ensuring the safety of their respective products.[23]

	Fractionation						Exchange Chromatography					Filtration				
	Cohn-Oncley	Cohn-Oncley cold ethanol	Kistler & Nitschman	Cold alcohol	Octanoic acid	Polyethylene glycol precipitation	Ion	DEAE-Sephadex	Anion	Caprylate precipitation, filtration	Chromatography, unspecified	Nanofiltration	Cloth	Depth	Ultra-filtration	Solvent/detergent treatment
Intravenous																
Bivigam	x			x					x			x[a]				x
Carimune NF, Nanofiltered[b,c]			x									x		x		
Flebogamma DIF 5% and 10%[b,d]				x		x	x					x[e]				
Gammagard S/D		x					x									x
Gammaplex[f]			x					x[g]				x[h]				x
Octagam		x									x				x	x
Privigen[b,c]				x	x[i]						x	x		x		
Intravenous or Subcutaneous																
Gammagard Liquid[j]		x					x					x[a]				x
Gammaked[f]	x									x			x	x		
Gamunex-C[f]	x									x			x	x		
Subcutaneous Only																
Cuvitru[j,k]		x					x		x			x[a]				x
Hizentra[b,c,k]				x	x				x			x		x		
Hyqvia[j]		x					x					x[a]				x

Table 2. Production methods.[24,25] Adapted from Characteristics of Immune Globulin Products Used to Treat Primary Immunodeficiency Diseases, 2016 January.

[a]35 nm; [b]pH 4 incubation; [c]undergoes additional reduction steps; [d]undergoes pasteurization; [e]sequential nanofiltration (35 and 20 nm); [f]also undergoes low pH incubation; [g]also undergoes CM-Sepharose chromatography; [h]20 nm virus filtration; [i]also undergoes CH9 filtration; [j]also undergoes low pH/elevated temperature incubation; [k]also undergoes other virus filtration

Immune globulin product selection should be guided by patient specific characteristics. The route of administration is an important consideration and can impact product selection. Different immune globulin products also use different additives to stabilize their products. Some of these additives may be detrimental to patients with certain concurrent medical conditions. For example, products stabilized with sucrose may be inappropriate for diabetic patients while products stabilized with certain amino acids may need to be avoided in patients with certain metabolic conditions. The sodium content may also be a consideration in patients with heart failure. Table 3 outlines the variety of additives in each of the products and the relative comorbid conditions that may be impacted by the use of the product. The greatest number of adverse reactions from the use of Ig have been logged as a result of patients switching between products.[26,27] AAAI and Clinical Immunology Society both support the use of individualized patient characteristic considerations and direct physician consultation in all situations of product selection.[28,29]

Selection of product is largely a function of matching patient characteristics with product properties. With the availability of both intravenously- and subcutaneously-administered products, physicians have a broader repertoire from which to choose for their patients. It is important to consider the appropriate utilization of donated plasma products due to the overall limited resource from which to harvest it. A recent article attempts to address this issue by proposing a preliminary framework for prioritizing the use of therapeutic immune globulin for various indications.[30] Managing demand with supply utilizing evidence-based means works to ensure prudent use of such a resource.

		Liquid	Lyophilized	Sugar Content	Sodium Content	Osmolarity/ Osmolality (mOsm/kg)	pH	IgA Content (mcg/mL)
Intravenous								
Bivigam		x		no added sugars	0.1–0.14 mol/L NaCl	< 510	4–4.6	≤ 200
Carimune NF, Nanofiltered			x	1.67 gm sucrose* per gram of protein	< 20 mg NaCl per gram protein	3% NS 498; 6% NS 690; 9% NS 882; 12% NS 1,074; 3% D5W 444; 6% D5W 636; 9% D5W 828; 12% D5W 1,020; 3% SW 192; 6% SW 384; 9% SW 576; 12% SW 768	6.4–6.8	720
Flebogamma DIF	5%	x		none	trace amounts	240–370	5–6	Average: < 3 Spec. value: < 50
	10%							Average: < 3 Spec. value: < 10
Gammagard S/D	5%		x	20 mg/mL glucose	8.5 mg/mL NaCl	636	6.8 ± 0.4	≤ 1
	10%		x	40 mg/mL glucose	17 mg/mL NaCl	1,250		≤ 2.2
Gammaplex		x		5% D-sorbitol (polyol)	30–50 mmol/L	460–500	4.6–5.1	Average: < 4 Spec. value: < 10
Octagam	5%	x		100 mg/mL maltose	≤30 mmol/L	310–380	5.1–6	< 100
	10%	x		90 mg/mL maltose	≤30 mmol/L	310–380	4.5–5	~106
Privigen	5%	x		none	trace amounts	isotonic (320)	4.8	≤ 25
	10%							
Intravenous or Subcutaneous								
Gammagard Liquid (IV, SC)		x		no added sugars	no added sodium	240–300	4.6–5.1	37
Gammaked (IV, SC)		x		none	trace amounts	258	4–4.5	46
Gamunex-C (IV, SC)		x		none	trace amounts	258	4–4.5	46
Subcutaneous Only								
Cuvitru		x		no added sugars	no added sodium	280–292	4.6–5.1	80
Hizentra		x		none	trace amounts (≤10 mmol/L)	380	4.6–5.2	≤ 50
Hyqvia†		x		no added sugars	no added sodium	240-300	4.6–5.1	37

Table 3. Physicochemical properties. NaCl, sodium chloride; nr, not reported; NS, normal saline; D5W, 5% dextrose in water; SW, sterile water. Adapted from Characteristics of Immune Globulin Products Used to Treat Primary Immunodeficiency Diseases; March, 2013.[31,32]

*Sucrose does not require compensatory changes to insulin regimens; excreted unchanged in urine.[33]

†In addition to the immune globulin 10% preparation, Hyqvia also contains a vial of recombinant human hyaluronidase genetically engineered utilizing Chinese Hamster Ovary (CHO) cells. The purified hyaluronidase has an approximate pH of 7.4 and an osmolality of 290 to 350 mOsm. Each vial contains 160 units (U)/mL of recombinant human hyaluronidase with 8.5 mg/mL sodium chloride, 1.78 mg/mL, sodium phosphate dibasic dihydrate, 1 mg/mL human albumin, 1 mg/mL edentate disodium dihydrate, 0.4 mg/mL calcium chloride dihydrate, and 0.17 mg/mL sodium hydroxide added for pH adjustment.

Treatment Guidelines

The AAAI released a list of 8 guiding principles in December 2011 to support the safe and effective use of therapeutic immunoglobulin.[34]

Principles	Description
Indication	IVIG is FDA indicated for use in primary immunodeficiency where antibody production is absent or deficient
Diagnoses	Primary immunodeficiency has varied phenotypic manifestations. IVIG is indicated and recommended for the following clinical situations: A. Primary immune defects with absent B cells B. Primary immune defects with hypogammaglobulinemia and impaired specific antibody production C. Primary immune defects with normogammaglobulinemia and impaired specific antibody production
Frequency of Treatment	Once a diagnosis is confirmed, interruption of treatment places the patient at significant risk IVIG administration should occur at every 3 to 4 week intervals to ensure adequate coverage Due to patient specific factors, shorter intervals may need to be considered
Dose	IVIG indicated for PI is supported by initial starting doses of 400 to 600 mg/kg every 3 to 4 weeks; alternate regimens are not supported by clinical literature
IgG Trough Levels	Interpretations of trough levels are only applicable in a subset of patients whose condition is characterized by low quantities of IgG levels For patients with sufficient quantities of IgG but who have impaired quality, trough levels are not correlated to clinical benefit Trough levels, as a rule, should be maintained above 500 mg/dL
Site of Care	Clinical characteristics and stability of the patient within a particular regimen should guide the decision for where IVIG is administered
Route	The use of the subcutaneous (SC) versus intravenous (IV) route to administer immunoglobulin therapy relies on a variety of patient characteristics. Some benefit of SC administration may be afforded to patients with poor venous access as well as those with difficult to control adverse reactions using the IV route
Product	IVIG is not an interchangeable product Product selection relies heavily on clinical discretion to match the appropriate product to the patient while considering various patient factors, including comorbidities

Table 4. The AAAAI's 8 guiding principles for effective use of IVIG for patients with primary immunodeficiency.[35]

PHARMACOLOGY[36,37,38,39,40,41,42,43,44,45,46,47,48,49,50]

Commercially available immune globulins supply IgG antibodies capable of opsonizing and neutralizing a wide variety of bacterial pathogens, thus augmenting the patient's ability to fight foreign offenders. Additional immune globulin subtypes may be present in the formulations that may interact with erythrocytes and other immune cells thereby altering the activity of these cells. These secondary mechanisms of action have not been fully elucidated.

PHARMACOKINETICS[51,52,53,54,55,56,57,58,59,60,61,62,63,64,65]

Drug	Dose	Bioavailability (%)	Elimination Half-life (days)	Mean Trough (mg/dL)
Intravenous				
Bivigam	300–800 mg/kg/4 weeks	n/a	33.5	1,106
Carimune NF, Nanofiltered	nr	n/a	nr	nr
Flebogamma DIF 5% and 10%	496 mg/kg/4 weeks	n/a	37	87.7
Gammagard Liquid, IV	455 mg/kg/4 weeks (median)	n/a	35	1,030
Gammagard S/D	460 mg/kg	n/a	37.7	1,186
Gammaplex	468 mg/kg/4 weeks	n/a	5.96	nr
Gamunex-C, IV Gammaked, IV	100–600 mg/kg ≈	n/a	35.74	780
Octagam	300–600 mg/kg	n/a	40.7	763.5
Privigen	200–714.3 mg/kg/4 weeks	n/a	45.4	1,000
Subcutaneous				
Cuvitru	Individualized by trough IgG	nr	nd	1,474
Gammagard, SC	183 mg/kg/week*	nd	nd	1,202
Gamunex-C, SC Gammaked, SC	total weekly IVIG dose multiplied by 1.37 and divided by previous dosing interval†	nr	nd	1,140
Hizentra, SC	228 mg/kg/week	nd	nd	1,448
Hyqvia	134 to 160 mg/kg/week	93.3‡	59.3	1,077

nd = no data, nr= not reported

*The subcutaneous dose of Gammagard liquid required to provide an area under the curve (AUC) exposure that is not inferior to IV Gammagard liquid is 137% of the intravenous dose for subjects 12 years of age and over.

† The subcutaneous doses of Gammaked and Gamunex-C required to provide an AUC exposure that is not inferior to their respective IV administrations is calculated by multiplying the total IV dose by 1.37 and then dividing by the weekly interval (3 or 4) of the previous IV administration frequency.

≈Doses listed are those studied in pharmacokinetic analysis and may not reflect current dosing recommendations. Refer to the Dosages table for current dosage and administration.

‡ Relative to IVIG.

CONTRAINDICATIONS/WARNINGS[66,67,68,69,70,71,72,73,74,75,76,77,78,79,80]

Contraindications

All immune globulin products are contraindicated in individuals with a history of severe anaphylaxis to such preparations and in individuals with known antibodies to IgA with selective immunoglobulin A deficiency (IgA < 0.05 gm/L).

Gammaplex is contraindicated in patients with a hereditary intolerance to fructose or infants and neonates with non-established sucrose or fructose tolerance.

Hyqvia is contraindicated in patients with known hypersensitivity to hyaluronidase, recombinant human hyaluronidase, or any excipients.

Warnings

Labels for all intravenous, subcutaneous, and intramuscular immune globulin products were updated in 2013 to include a boxed warning regarding the risk of thrombosis with these products. Risk factors for thrombosis include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in patients without identified risk factors. In patients with thrombosis risk factors, administration should occur at the minimum dose and infusion rate that is practical and adequate hydration should be ensured prior to administration. Patients should be monitored for hyperviscosity and signs or symptoms of thrombosis; patients should be instructed to immediately report symptoms of thrombosis. In patients at risk for hyperviscosity, an assessment of blood viscosity should be considered.

All intravenous immune globulin products contain a boxed warning of acute renal dysfunction and failure. Geriatric individuals over the age of 65 are at an increased risk. Administration should proceed at the minimum infusion rate practical and these products should be discontinued if renal function deteriorates. Cuvitru labeling also carries a warning (not a boxed warning) for renal dysfunction and/or renal failure.

Anaphylaxis and severe hypersensitivity are significant risks particularly for IgA deficient individuals who possess antibodies to IgA. Medications such as epinephrine should be immediately available. All patients receiving immune globulin for the first time, who are switching from one product to another, or who have not received the immune globulin for at least eight weeks should be monitored in a clinical setting for signs of fever, chills, nausea, vomiting, and shock.

Intravenous products may cause hyperproteinemia due to increased serum viscosity and may result in hyponatremia. Thromboembolic events have been reported.[81] Monitor patients, particularly those individuals at risk of hyperviscosity.

Transfusion-related acute lung injury (TRALI) may occur as a result of immune globulin therapy. Evaluate patients with suspected lung injury for antineutrophil antibodies (ANA).

Acute intravascular hemolysis and hemolytic anemia are risks of immune globulin therapy. Risk factors include blood type (non-O serotypes) and high doses.

Subcutaneous products, unless specifically indicated, must not be injected directly into a blood vessel.

Aseptic meningitis syndrome has been reported with immune globulin products, particularly with rapid infusion or high doses.

Therapeutic immune globulin products are isolated from human plasma and may pose a risk to the patient of exposure to infectious agents such as viruses and, theoretically, prions. This also applies to unknown or emerging viruses and other pathogens. There is a theoretical risk for the transmission of Creutzfeldt-Jakob disease (CJD) agent although no cases of transmission due to immune globulin products have been identified.

Due to the passively transferred antibodies, false positive serologic testing may occur transiently. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect Coombs test.

Volume overload may be a risk when large volumes of lower concentration intravenous immune globulin solutions are administered.

Subcutaneous infusion into or around an infected area can result in the spread of a localized infection. Hyqvia should not be infused into these areas due to the potential risk of spreading a localized infection.

Privigen is contraindicated in individuals with hyperprolinemia due to the presence of L-proline, a stabilizer.

Patients receiving Hyqvia may develop non-neutralizing antibodies to the recombinant human hyaluronidase component. The potential exists for these antibodies to cross-react with endogenous PH20, which is known to be expressed in the adult male testes, epididymis and sperm. It is unknown whether these antibodies may interfere with fertilization in humans; the clinical significance of these antibodies is not known.

Do not administer immune globulins subcutaneously in patients with ITP because of the risk of hematoma formation.

Agents derived from human blood carry a risk of transmitting infectious agents; production methods, as described above, are used to minimize this risk.

DRUG INTERACTIONS[82,83,84,85,86,87,88,89,90,91,92,93,94,95,96]

Immune globulin products should not be mixed or co-administered with any other products.

Lyophilized products should only be reconstituted with the solutions outlined in the package inserts.

Exogenous immune globulin may alter an individual's response to live virus vaccines such as measles, mumps, rubella, and varicella. Serological test results may be confounded.

Octagam contains maltose which may interfere with blood glucose test units that do not employ a glucose-specific method of testing.

Admixtures of Hyqvia with other drug solutions have not been evaluated. Hyqvia should not be mixed or administered with any other products.

ADVERSE EFFECTS[97,98,99,100,101,102,103,104,105,106,107,108,109,110,111]

In Adults

Drug	Number of Infusions -- Number of Subjects	Injection site/ Infusion reaction # (rate)	Number (Rate) of infusions with adverse event							
			Headache	GI Disorder, Diarrhea, etc.	Fatigue	Rash/ Urticaria	Abdominal Pain/ Discomfort	Arthralgia	Nausea	Tachycardia
Intravenous										
Bivigam	746 -- 63	5 (0.007)	115 (0.154)	nr	59 (0.079)	nr	nr	nr	8 (0.011)	nr
Carimune NF	nr	nr	(0.02)	nr	nr	reported	nr	reported	nr	nr
Flebogamma DIF	nr	nr	reported	nr	nr	nr	nr	reported	reported	reported
Gammagard S/D	nr	nr	(0.051 – 0.109)	3 (0.014)	(0.01 – 0.052)	1 (0.003)	3 (0.014)	reported	(0.015 – 0.066)	reported
Gammagard liquid, IV	1812 -- 61	nr	94 (0.052)	12 (0.007)	33 (0.018)	6 (0.003)	nr	5 (0.003)	17 (0.009)	nr
Gammaplex	703 -- 50	nr	53 (0.075)	nr	9 (0.013)	nr	nr	nr	7 (0.01)	nr
Gamunex-C, IV Gammaked, IV	825 -- 87	nr	57 (0.069)	nr	nr	5 (0.06)	nr	nr	31 (0.038)	nr
Octagam 5%	654 -- 46	11 (0.02)	62 (0.09)	22 (0.03)	9 (0.01)	8 (0.01)	(0.005 – 0.02)	15 (0.02)	8 (0.01)	reported
Octagam 10%	nr -- 54	nr	25	reported	reported	reported	reported	reported	reported	reported

Adverse Effects (continued)

Drug	Number of Infusions -- Number of Subjects	Injection site/ Infusion reaction # (rate)	Number (Rate) of infusions with adverse event							
			Headache	GI Disorder, Diarrhea, etc.	Fatigue	Rash/ Urticaria	Abdominal Pain/ Discomfort	Arthralgia	Nausea	Tachycardia
Intravenous *(continued)*										
Privigen	771 -- 55	nr	56 (0.073)	nr	nr	nr	4 (0.005)	nr	10 (0.013)	nr
Subcutaneous										
Cuvitru	4327 -- 74	96 (0.022)	50 (0.012)	5 (0.001)	9 (0.002)	nr	reported	reported†	16 (0.004)	reported
Gammagard liquid, SC	2294 -- 47	55 (0.024)	31 (0.014)	5 (0.002)	11 (0.005)	nr	9 (0.004)	nr	7 (0.003)	11 (0.005)
Gamunex-C, SC Gammaked, SC	725 -- 32	24 (0.75)	4 (0.13)	nr	2 (0.063)	nr	nr	2 (0.063)	nr	nr
Hizentra	2264 -- 49	1322 (0.584)	32 (0.014)	6 (0.003)	4 (0.002)	nr	3 (0.001)	3 (0.001)	4 (0.002)	nr
Hyqvia*	1,129 -- 81	234 (0.21)	40 (0.04)	nr	16 (0.01)	nr	nr	nr	12 (0.01)	nr

Adverse effects data are obtained from prescribing information and, therefore, should not be considered comparative or all inclusive. Rate is reported in parentheses.

*Adverse reaction data in 81 subjects included both adult and pediatric patients. A total of 15 out of 83 subjects who were treated with Hyqvia developed an antibody capable of binding to recombinant human hyaluronidase in the clinical trials. These antibodies were not capable of neutralizing recombinant human hyaluronidase. No temporal association between adverse reactions and the presence of antibodies capable of binding to the Recombinant Human Hyaluronidase could be demonstrated. There was no increase in incidence or severity of adverse reactions in subjects who developed antibodies to Recombinant Human Hyaluronidase and in all subjects, antibody titers decreased despite continued treatment.

† Arthralgia was reported in 5 of 2,349 infusions with 48 subjects (rate = 0.002) in a European study.

SPECIAL POPULATIONS[112,113,114,115,116,117,118,119,120,121,122,123,124,125,126]

Pediatrics

Gammaplex is indicated for replacement therapy in patients 2 years of age and older with primary humoral immunodeficiency (PHI). This is based on data in 31 patients aged 2 to 16 years. It is not indicated in pediatric patients with chronic immune thrombocytopenia purpura. While safety has been established in 31 pediatric patients, the number of patients with efficacy data (2 children aged 6 years; 1 aged 12 years) is too small to establish use in this population.

Flebogamma 5% DIF has been determined to be efficacious for the prevention of serious bacterial infections in children with PI aged 2 to 16 years. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. Safety and efficacy of Flebogamma 5% DIF in pediatric patients below the age of 2 years has not been established.

Only 3 pediatric patients with PHI I (2 children between the ages of 6 and 10, and 1 child 16 years old) were included in the clinical evaluation of Flebogamma 10% DIF. This number of subjects is too small to establish safety and efficacy in the pediatric population. Flebogamma 10% DIF is approved for the treatment of chronic primary immune thrombocytopenia in patients 2 years of age and older.

Bivigam has been studied in children with PHI over 6 years of age. No differences in dosing requirements were determined. The safety and effectiveness of Bivigam has not been established in pediatric patients with PI who are under the age of 6.

Gammagard S/D is indicated as replacement therapy for primary humoral immunodeficiency (PI) in pediatric patients 2 years of age or older. Clinical studies of Gammagard S/D for the treatment of PI did not include sufficient numbers of subjects who were 16 or under to determine whether they respond differently from adults. Efficacy and safety of Gammagard S/D in pediatric patients with chronic immune thrombocytopenic purpura (ITP) has not been established. Efficacy and safety of Gammagard S/D in pediatric patients with Kawasaki disease has been established with the majority of these patients being under 5 years of age and 20% of these patients under 1 year of age.

The safety and efficacy profiles for children ages 2 and older for Gammagard liquid (IV or SC administration) are similar to adult subjects. Safety and efficacy of Gammagard liquid in patients below the age of 2 have not been established.

Privigen was evaluated in 31 pediatric subjects (19 children and 12 adolescents) with PI (pivotal study). There were no apparent differences in the safety and efficacy profiles as compared to those in adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. The safety and effectiveness of Privigen have not been established in pediatric patients with PI who are under the age of 3. The safety and effectiveness of Privigen have not been established in pediatric patients with chronic ITP who are under the age of 15.

Pharmacokinetics, safety and efficacy of Gamunex-C in PI or SC were similar to those in adults with the exception that vomiting and fever were more frequently reported in pediatrics (3 of 18 subjects in PI IV study for vomiting; 6 of 12 subjects in ITP SC study). No pediatric-specific dose requirements were necessary to achieve serum IgG levels. Gamunex-C SC was evaluated in 14 pediatric subjects (age range, 2 to 16 years) with PI. Gamunex-C is approved for treatment of PI and ITP in pediatrics ages 2 years and older. It is not approved in pediatrics with chronic inflammatory demyelinating polyneuropathy.

Data with Gamunex-C have been extrapolated to Gammaked.

Hizentra in both the weekly dosing schedule and the biweekly dosing schedule have safety and effectiveness data in the pediatric age groups 2 to 16, as supported by evidence from adequate and well-controlled studies. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. Safety and effectiveness in children under the age of 2 has not been established.

Administration of Carimune in pediatric patients with acute or chronic Immune Thrombocytopenic Purpura did not reveal any pediatric-specific hazard.

Octagam 5% liquid was evaluated in 11 pediatric subjects (age range, 6 to 16 years). There were no obvious differences observed between adults and pediatric subjects with respect to pharmacokinetics, efficacy and safety. No pediatric specific dose requirements were necessary to achieve the desired serum IgG levels. The safety and efficacy of Octagam 10% in pediatric patients with chronic ITP has not been established.

Safety of Hyqvia in children has not been established.

Cuvitru is approved for use in patients 2 years of age and older. It was evaluated in 21 patients (age range, 2 to 16 years) with PI and efficacy and safety findings were similar to those found in adults.

Geriatrics

Insufficient numbers of geriatric patients (older than 65 years of age) were enrolled in most trials. While no differences in safety and efficacy were observed in any trial, there are insufficient data to determine whether geriatric patients respond differently than younger subjects. For individuals over the age of 65, or for any patients at risk of developing renal insufficiency, it is advised that the recommended dose is not exceeded. The product should be infused at the minimum practical infusion rate.

Pregnancy

All products included in this review are Pregnancy Category C with the exception of Cuvitru. Cuvitru has not been assigned a Pregnancy Category based on the Pregnancy and Lactaction Labeling Rule (PLLR); rather, it caries only descriptive information. No human data on Cuvitru are available to evaluate the drug-associated risk, but immune globulins can cross the placenta after 30 weeks of gestation.

Hepatic/Renal Impairment

Individuals at risk for renal insufficiency are at increased risk for renal complications with the use of immune globulin.

DOSAGES[127,128,129,130,131,132,133,134,135,136,137,138,139,140,141]

Please consult drug labeling for specific dosing adjustment recommendations.

Drug	Dose				Availability
	Dx	Dose	Initial Infusion Rate	Maintenance Infusion Rate	
General Guidance, intravenous (IV)	▪ Refer to each product's package insert for special considerations for each product ▪ Use caution in pre-existing renal insufficiency; ensure patients are not volume depleted ▪ Administer at minimum infusion rate practical for patients at risk of renal dysfunction or thrombotic events ▪ Do not infuse or mix with other medications; administer via dedicated line ▪ Doses are in body weight (BW)				
Bivigam, *IV*	PI	300–800 mg/kg every 3–4 weeks	0.5 mg/kg/min for first 10 minutes	Increase every 20 min (if tolerated) by 0.8 mg/kg/min up to 6 mg/kg/min	▪ 10% vial, 50 mL ▪ 10% vial, 100 mL
Carimune NF, Nanofiltered, *IV*	PI	400–800 mg/kg every 3–4 weeks	0.5 mg/kg/min for first 10 minutes	Increase every 30 min (if tolerated) by 1 mg/kg/min up to max 3 mg/kg/min	▪ 6 gm vial, lyophilized ▪ 12 gm vial, lyophilized
	ITP	Induction therapy: 400 mg/kg on 2–5 consecutive days	0.5 mg/kg/min for first 10 minutes	Increase every 30 min (if tolerated) by 1 mg/kg/min up to max 3 mg/kg/min	
		▪ Only 2 consecutive doses are required if the initial platelet count response to first 2 doses is adequate (30–50,000/µL) ▪ For chronic ITP, if platelet counts fall to < 30,000/µL or there is significant bleeding, patient may be given a 400 mg/kg dose as a single infusion; dose may be increased to 800–1,000 mg/kg if response is inadequate			
	▪ In PI treatment naive patients, the first dose must be given as a 3% immunoglobulin solution; subsequent doses may be given at higher concentrations if tolerated ▪ Administer at minimum infusion rate practical for patients at risk of renal dysfunction or thrombotic events; do not infuse at a rate greater than 2 mg/kg/min ▪ Recommended concentration for ITP is 6%				
Flebogamma DIF, *IV*	PI	300–600 mg/kg every 3–4 weeks	0.5 mg/kg/min (5%) or 1 mg/kg/min (10%)	Increase to (if tolerated) a max of 5 mg/kg/min (5%) or 8 mg/kg/min (10%)	▪ 5% vial, 10 mL ▪ 5% vial, 50 mL ▪ 5% vial, 100 mL ▪ 5% vial, 200 mL ▪ 5% vial, 400 mL ▪ 10% vial, 50 mL ▪ 10% vial, 100 mL ▪ 10% vial, 200 mL
	ITP	1 gm/kg daily for 2 consecutive days	1 mg/kg/min (10% only)	If tolerated, increase to a max of 8 mg/kg/min (10%)	

Dosages (continued)

Drug	Dose				Availability
	Dx	Dose	Initial Infusion Rate	Maintenance Infusion Rate	
Gammagard Liquid, *IV*	PI	300–600 mg/kg every 3–4 weeks based on clinical response	0.5 mL/kg/hr (0.8 mg/kg/min) for 30 min	Increase up to 5 mL/kg/hr (8 mg/kg/min) every 30 minutes if tolerated	▪ 10% vial, 10 mL ▪ 10% vial, 25 mL ▪ 10% vial, 50 mL ▪ 10% vial, 100 mL ▪ 10% vial, 200 mL ▪ 10% vial, 300 mL
	MMN	0.5–2.4 gm/kg per month based on clinical response	0.5 mL/kg/hr (0.8 mg/kg/min)	Infusion rate may be advanced to 5.4 mL/kg/hr (9 mg/kg/min) if tolerated	
	▪ Indicated for 2 years of age and older ▪ MMN, multifocal motor neuropathy				
Gammagard S/D, *IV*	PI	300–600 mg/kg every 3–4 weeks	5%: 0.5 mL/kg/hr 10%: 0.5 mL/kg/hr	5%: may increase gradually as tolerated to a maximum of 4 mL/kg/hr (patients who tolerate this rate can be infused with the 10% concentration starting at 0.5 mL/kg/hr) 10%: may increase gradually as tolerated to a maximum of 8 mL/kg/hr	▪ 5 gm ▪ 10 gm
	ITP	1 gm/kg for a maximum of 3 doses on alternate days			
	CLL	400 mg/kg every 3–4 weeks			
	KS	Single dose of 1 gm/kg OR a daily dose of 400 mg/kg on 4 consecutive days			
	▪ Kawasaki syndrome (KS); administer concomitant aspirin therapy of 80–100 mg/kg/day in 4 divided doses ▪ Begin therapy for KS within 7 days of fever onset ▪ A maximum infusion rate of 3.3 mg/kg/min should be used in patients at risk for renal dysfunction or thrombotic complications				
Gammaplex, *IV*	PI	300–800 mg/kg every 3–4 weeks	0.5 mg/kg/min for (0.01 mL/kg/min) for 15 minutes	Increase up to max of 4 mg/kg/min (0.08 mL/kg/min)	▪ 5% vial, 100 mL ▪ 5% vial, 200 mL ▪ 5% vial, 400 mL
	ITP	1 gm/kg for 2 consecutive days	0.5 mg/kg/min for (0.01 mL/kg/min) for 15 minutes	Increase up to max of 4 mg/kg/min (0.08 mL/kg/min)	
	▪ Insufficient data exists on the efficacy of Gammaplex using a low dose regimen (400 mg/kg per day for 5 consecutive days) in ITP				

Dosages (continued)

Drug	Dose				Availability
	Dx	Dose	Initial Infusion Rate	Maintenance Infusion Rate	
Gamunex-C, *IV;* Gammaked *IV*	PI	300–600 mg/kg every 3–4 weeks	1 mg/kg/min	8 mg/kg/min	▪ 1 gm/10 mL vial ▪ 2.5 gm/25 mL vial ▪ 5 gm/50 mL vial ▪ 10 gm/100 mL vial ▪ 20 gm/200 mL vial ▪ Gamunex-C only: 40 gm/400 mL
	ITP	2 gm/kg	1 mg/kg/min	8 mg/kg/min	
	CIDP	Loading dose: ▪ 2 gm/kg Maintenance: ▪ 1 gm/kg every 3 weeks	2 mg/kg/min	8 mg/kg/min	
	▪ Contains glycine to manage isotonicity				
Octagam, *IV*	PI	5%: 300–600 mg/kg every 3–4 weeks	0.5 mg/kg/min for the first 30 min	Increase to 1 mg/kg/hr for 30 min; advance to 2 mg/kg/min for third 30 minutes; may increase by 0.5 mg/kg/hr up to max of 3.3 mg/kg/min	▪ 5% vial, 20 mL ▪ 5% vial, 50 mL ▪ 5% vial, 100 mL ▪ 5% vial, 200 mL ▪ 5% vial, 500 mL
	chronic ITP	1 g/kg for 2 consecutive days	1 mg/kg/min	May double infusion rate every 30 minutes up to 12 mg/kg/min	▪ 10% bottle, 20 mL ▪ 10% bottle, 50 mL ▪ 10% bottle, 100 mL ▪ 10% bottle, 200 mL
Privigen, *IV*	PI	200–800 mg/kg every 3–4 weeks	0.5 mg/kg/min (0.005 mL/kg/min)	Increase up to max of 8 mg/kg/min (0.08 mL/kg/min)	▪ 10% vial, 50 mL ▪ 10% vial, 100 mL ▪ 10% vial, 200 mL ▪ 10% vial, 400 mL
	chronic ITP	1 g/kg for 2 consecutive days	0.5 mg/kg/min	Increase up to 4 mg/kg/min	
	ITP	1 gm/kg for 2 consecutive days	0.5 mg/kg/min (0.005 mL/kg/min)	Increase up to max of 8 mg/kg/min (0.08 mL/kg/min)	

Dosages (continued)

Drug	Dose				Availability
	Dx	Dose	Initial Infusion Rate	Maintenance Infusion Rate	
SUBCUTANEOUSLY (SC) ADMINISTERED PRODUCTS					
Cuvitru, *SC*	PI	Dose should be initially individualized based on pharmacokinetics and clinical response and subsequently by serum IgG trough levels (see prescribing information for details; administration frequency ranges from daily up to every 2 weeks **Multiply:** Previous IVIG dose (in grams) x 1.3; then divide by the number of weeks between intravenous doses; provides initial weekly dose, then adjust by desired frequency; initiate 1 week following prior IVIG dose	First 2 infusions ≥ 40 kg BW: ▪ ≤ 60 mL/site; ▪ 10–20 mL/hr/site < 40 kg BW: ▪ ≤ 20 mL/site; ▪ 10–20 mL/hr/site	≥ 40 kg BW: ▪ ≤ 60 mL/site; ▪ ≤ 60 mL/hr/site < 40 kg BW: ▪ ≤ 60 mL/site; ▪ ≤ 60 mL/hr/site	▪ 20% vial, 5 mL ▪ 20% vial, 10 mL ▪ 20% vial, 20 mL ▪ 20% vial, 40 mL ▪ Room temperature or refrigerated ▪ Latex-free

Dosages (continued)

Drug	Dose				Availability
	Dx	Dose	Initial Infusion Rate	Maintenance Infusion Rate	
SUBCUTANEOUSLY (SC) ADMINISTERED PRODUCTS					
Gammagard Liquid, *SC*	PI	**Multiply:** Previous IVIG dose (in grams) x 1.37; then divide by the number of weeks between intravenous doses	≥ 40 kg BW: ▪ 30 mL/site; ▪ 20 mL/hr/site < 40 kg BW: ▪ 20 mL/site; ▪ 15 mL/hr/site	≥ 40 kg BW: ▪ 30 mL/site; ▪ 20–30 mL/hr/site < 40 kg BW: ▪ 20 mL/site; ▪ 15–20 mL/hr/site	▪ 10% vial, 10 mL ▪ 10% vial, 25 mL ▪ 10% vial, 50 mL ▪ 10% vial, 100 mL ▪ 10% vial, 200 mL ▪ 10% vial, 300 mL
Gamunex-C, *SC;* Gammaked, *SC*	PI	**Multiply:** Previous IGIV dose (in grams) x 1.37; then divide by the number of weeks between intravenous doses	20 mL/hr/site; multiple simultaneous infusion sites may be utilized; the maximum number of infusion sites is 8 in adults and 6 in children; children should start at a slower infusion rate (see prescribing information for weight-based details)	Not determined	▪ 1 gm / 10 mL vial ▪ 2.5 gm / 25 mL vial ▪ 5 gm / 50 mL vial ▪ 10 gm / 100 mL vial ▪ 20 gm / 200 mL vial ▪ Gamunex-C only: 40 gm/400 mL vial
	▪ May not be administered SC for ITP or CIDP				
Hizentra, *SC*	**Initial Weekly Dose:** ▪ (Previous IVIG dose [in grams]/ Number of weeks between IVIG doses) x 1.37 **Additional notes:** ▪ Hizentra can be administered at regular intervals from daily up to every 2 weeks (biweekly) ▪ Administer first dose 1 week after receiving a regularly scheduled IVIG infusion ▪ Hizentra may be administered after the patient has received IVIG infusions at regular intervals for at least 3 months ▪ Provided the total weekly dose is maintained, any dosing interval from daily up to biweekly may be used for biweekly dosing, multiply the calculated Hizentra weekly dose by 2 ▪ For frequent dosing (2 to 7 times per week), divide the calculated weekly dose by the desired number of times per week (e.g. for 3 times per week dosing, divide weekly dose by 3) ▪ Infuse via an infusion pump ▪ Rotate administration sites weekly (abdomen, thighs, upper arms, and/or lateral hip); may use up to 4 injection sites simultaneously or up to 12 sites consecutively per infusion; minimum 2 inches between sites ▪ Infusion volume – for the first infusion, up to 15 mL per injection site; this may be increased to 20 mL per site after the fifth infusion and to a maximum of 25 mL per site as tolerated ▪ Infusion rate – for the first infusion, up to 15 mL/hr per site; this may be increased, to a maximum of 25 mL/hr per site as tolerated ▪ Must **NOT** be administered intravenously				▪ 1 gm/5 mL vial ▪ 2 gm/10 mL vial ▪ 4 gm/20 mL vial ▪ 10 gm/50 mL vial ▪ Single-use, tamper-evident vial ▪ Preservative-free; latex-free ▪ Room temperature

Dosages (continued)

<table>
<tr><th>Drug</th><th>Dose</th><th>Availability</th></tr>
<tr><td>Hyqvia,
SC</td><td>
Dosing:
For patients previously treated with another IgG treatment, administer the first dose approximately one week after the last infusion of their previous treatment
Initial Treatment Interval/Ramp-up Schedule:
<table>
<tr><th>Week</th><th>Infusion</th><th>Dose/Interval</th><th>Example:
30 grams/4 weeks</th></tr>
<tr><td>1</td><td>1st infusion</td><td>1-week-dose</td><td>7.5 grams</td></tr>
<tr><td>2</td><td>2nd infusion</td><td>2-week-dose</td><td>15 grams</td></tr>
<tr><td>3</td><td colspan="3">No Infusion</td></tr>
<tr><td>4</td><td>3rd infusion</td><td>3-week-dose</td><td>22.5 grams</td></tr>
<tr><td>5</td><td colspan="3">No Infusion</td></tr>
<tr><td>6</td><td colspan="3">No Infusion</td></tr>
<tr><td>7</td><td>4th infusion
(if required)</td><td>4-week-dose</td><td>30 grams</td></tr>
</table>
For patients switching from Immune Globulin Intravenous (IGIV):
▪ Administer Hyqvia at the same dose and frequency as the previous intravenous treatment, after the initial dose ramp-up
For patients naïve to IgG treatment or switching from another subcutaneous Immune Globulin (IGSC):
▪ Administer Hyqvia at 300 to 600 mg/kg at 3 to 4 week intervals, after initial ramp up
Administration:
▪ Hyqqvia should be administered by a healthcare professional, caregiver or self-administered by the patient after appropriate training
▪ Infusion requires an infusion pump meeting flow rate specifications and a subcutaneous 24 gauge needle set labeled for high flow rates
▪ Suggested sites for infusion are the abdomen and thighs; if two infusion sites are used , the two infusion sites should be on opposite sides of the body
▪ The two components must be infused sequentially, beginning with the Recombinant Human Hyaluronidase and then infusing the full dose of Immune Globulin 10% through the same subcutaneous needle set within approximately 10 minutes of the Recombinant Human Hyaluronidase infusion
▪ Rate of infusion:
▪ Administer the Recombinant Human Hyaluronidase at an initial rate of approximately one to two mL per minute, or as tolerated
Immune Globulin Infusion Rate:
<table>
<tr><th></th><th colspan="2">First Two Infusions</th><th colspan="2">Subsequent 2 or 3 Infusions</th></tr>
<tr><th></th><th>< 40 kg</th><th>≥ 40 kg</th><th>< 40 kg</th><th>≥ 40 kg</th></tr>
<tr><td>Intervals (minutes)</td><td>Rate per site (mL/ hour)</td><td>Rate per site (mL/hour)</td><td>Rate per site (mL/hour)</td><td>Rate per site (mL/hour)</td></tr>
<tr><td>5-15</td><td>5</td><td>10</td><td>10</td><td>10</td></tr>
<tr><td>5-15</td><td>10</td><td>30</td><td>20</td><td>30</td></tr>
<tr><td>5-15</td><td>20</td><td>60</td><td>40</td><td>120</td></tr>
<tr><td>5-15</td><td>40</td><td>120</td><td>80</td><td>240</td></tr>
<tr><td>Remainder of infusion</td><td>80</td><td>240</td><td>160</td><td>300</td></tr>
<tr><td>Remainder of infusion</td><td>80</td><td>240</td><td>160</td><td>300</td></tr>
</table>
</td><td>
▪ Dual vial unit of 2 single use vials; 1 vial containing immune globulin 10% and 1 vial containing recombinant human hyaluronidase
▪ 2.5 gm (25 mL) IG/200 units (1.25 mL) hyaluronidase
▪ 5 gm (50 mL) IG/400 units (2.5 mL) hyaluronidase
▪ 10 gm (100 mL) IG/800 units (5 mL) hyaluronidase
▪ 20 gm (200 mL) IG /1,600 units (10 mL) hyaluronidase
▪ 30 gm (300 mL) IG /2,400 units (15 mL)hyaluronidase
</td></tr>
</table>

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by the manufacturers. The search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance. Only clinical trials involving subcutaneous administration of immune globulin for the treatment of primary immunodeficiency are included in this review.

subcutaneous – therapeutic switch

A 40-week prospective, open-label, multicenter, single-arm, phase 3 study, enrolled 51 patients with PI.[142] Participants were switched from their current IV or SC regimens to weekly SC infusions of Hizentra at equivalent doses. Primary efficacy was measured as IgG levels prior to next infusion. IgG trough levels maintained similar concentrations between both the pre-study and efficacy portion of the study (7.49 [SD, 1.57] and 8.1 [SD, 1.34], respectively). Secondary efficacy was determined by the rate of serious bacterial infections (SBI). No SBI were identified during the efficacy period. For non-SBI infections, participants experienced a rate of 5.18 infections/patient/year (95% confidence interval [CI], 4.305 to 6.171). No serious adverse events were reported. Given the study design, extrapolation cannot be done to determine superiority.

A similarly structured study with 18 children and 5 adolescents was performed using Hizentra.[143] Again, no SBI were reported during the efficacy period and the overall infection rate was similar to the previous study with a rate of 4.77 infections/patient/year for the children and 5.18 infections/patient/year for the adolescent group. Three participants experienced serious adverse events (AE); 2 other recipients withdrew from the study due to 2 other AEs.

Forty-nine participants ages 3 to 77 years of age with a diagnosis of PI were enrolled in a multi-center, prospective, open-label study. The initial study period consisted of IV treatment with Gammagard liquid followed by a transition to SC administration with the same product at 137% of the IV dose. All SC doses were administered weekly. At the end of the assessment period, the mean trough IgG level was 1,202 mg/dL which is above the generally accepted level of 500 mg/dL. The overall infection rate was similar to other studies at 4.1 infections/patient/year; however, 3 serious acute bacterial infections did occur resulting in a rate of 0.067 SBI/patient/year. Minor localized infusion site reactions were observed, but in general, the product was reasonably well tolerated.

The limitation of all 3 studies continues to be the unknown subclassification of the participants' primary immunodeficiency. Given the overall low incidence of this umbrella of disease, it would be difficult to account for and study all subclassifications to minimize confounding elements inherent to the variability of the phenotypes.

A prospective, open-label, multicenter trial was conducted in the U.S. with 83 patients diagnosed with PIDD. The median age was 35 years (range, 4 to 78 years). All patients had received previous IV immune globulin therapy and 31 of the patients had received prior SC therapy. Planned outcome measures included the rate of infections, adverse reactions, tolerability of the Hyqvia infusions, number of infusion sites per month and infusion rate. All patients received hyaluronidase subcutaneous infusion. This was followed within 10 minutes by the immune globulin infusion. All patients followed a ramp-up schedule over 3 to 4 weeks to become familiar with the large volumes required for a full 3 or 4 week treatment. Subsequently, all patients continued the 3 or 4 week dosing for the remainder of the trial. After 3 doses at the full volume, a serum IgG trough level was obtained and used to adjust the Hyqvia dose if needed. All subjects who completed the trial received a minimum of 12 infusions at this individually adapted dose. The assessment period for efficacy and safety began after completion of the ramp-up initiation schedule and the length of therapy in the trial ranged from 42 to 507 days. None of the subjects withdrew due to a severe or serious local or systemic adverse reaction. There were 2 acute serious bacterial infections; both episodes of pneumonia. The annualized rate of acute serious bacterial infections while treated with Hyqvia was 0.025. A total of 78 of the 83 patients receiving Hyqvia (94%) attained the same 3 or 4 week dosing interval as compared to their previous IV immune globulin regimen and the monthly median infusion time was 3.2 hours for the intravenous immune globulin group and 2.64 hours for the Hyqvia group.

SUMMARY

Immune globulin products are derived from the pooled human plasma of thousands of donors. These products are purified to contain 95% to 99% IgG (the major antibody produced by B lymphocytes) with trace amounts of IgA and IgM. While all the products in the class have similar efficacy and safety profiles, they are not considered therapeutically equivalent due to differences in purification methods, the use of different chemical stabilizers, different physiochemical properties and differences in the recommended route of administration. The primary use for immune globulin therapy is the management of primary immunodeficiency disease (PIDD). Pooled IgG provides patients with passive immunity thereby decreasing the PIDD patient's risk of severe bacterial and viral infections. Immune globulin therapy for the treatment of PIDD is generally considered to be chronic therapy although some patients may be able to stop therapy at some point, according to physician discretion. Other FDA-approved indications for immune globulin therapy are idiopathic thrombocytopenic purpura (ITP), multifocal motor neuropathy, chronic inflammatory demyelinating polyneuropathy, B-cell chronic lymphocytic leukemia and the treatment of Kawasaki disease. Multiple IgG products are available for selection. The final product selection for a given patient should consider diagnosis, past product usage/tolerability, time since last dose, route of administration, individual risk factors for adverse events, comorbid conditions and the product's physicochemical properties. Reserving the use of immune globulin products for approved indications or conditions where the benefit has been clearly established and is consistent with clinical guidelines ensures that the most vulnerable patients have access to a limited resource.

REFERENCES

1 Bivigam [package insert]. Boca Raton, FL; Biotest; June 2013.
2 Carimune NF [package insert]. Kankakee, IL; CSL Behring; September 2013.
3 Flebogamma 10% [package insert]. Los Angeles, CA; Grifols; January 2016.
4 Flebogamma 5% [package insert]. Barcelona, Spain; Grifols; August 2014.
5 Gammagard S/D [package insert]. Westlake Village, CA; Baxter; September 2014.
6 Gammaplex [package insert]. Raleigh, NC; BP; July 2015.
7 Octagam 10% [package insert]. Hoboken, NJ; Octapharma; April 2015.
8 Octagam 5% [package insert]. Hoboken, NJ; Octapharma; October 2014.
9 Privigen [package insert]. Kankakee, IL; CSL Behring; December 2013.
10 Gammagard Liquid [package insert]. Westlake Village, CA; Baxter; September 2014.
11 Gammaked [package insert]. Fort Lee, NJ; Kedrion; September 2013.
12 Gamunex-C [package insert]. Research Triangle Park, NC; Grifols; December 2015.
13 Cuvitru [package insert]. Westlake Village, CA; Baxalta; September 2016.
14 Hizentra [package insert]. Kankakee, IL; CSL Behring; January 2015.
15 Hyqvia [package insert]. Westlake Village, CA; Baxter; April 2016.
16 Bonilla FA, Bernstein IL, Khan DA, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. Available at: https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/immunodeficiency2005.pdf. Accessed August 17, 2016.
17 Orange JS. Clinical update in immunoglobulin therapy for primary immunodeficiency diseases. 2011; 14: 1-12.Immune Deficiency Foundation. http://primaryimmune.org/wp-content/uploads/2011/04/Clinical-Update-in-Immunoglobulin-Therapy-for-Primary-Immunodeficiency-Diseases.pdf. Accessed August 17, 2016.
18 Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 2006; 117: S525–553.
19 Stiehm ER, Oragne JS, Ballow M, et al. Therapeutic use of immunoglobulins. Adv Pediatr. 2010; 57: 185–218.
20 Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 2006; 117: S525–553.
21 Orange JS. Clinical update in immunoglobulin therapy for primary immunodeficiency diseases. 2011; 14:1-12.Immune Deficiency Foundation. http://primaryimmune.org/wp-content/uploads/2011/04/Clinical-Update-in-Immunoglobulin-Therapy-for-Primary-Immunodeficiency-Diseases.pdf. Accessed August 17, 2016.
22 Zoon KC. Safety implications of fractionated blood products. http://www.fda.gov/newsevents/testimony/ucm114908.htm. Accessed August 17, 2016.
23 FDA. Guidance for industry: safety, efficacy, and pharmacokinetic studies to support marketing of immune globulin intravenous (human) as replacement therapy for primary humoral immunodeficiency. 2008 June. Rockville, MD. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm072130.htm. Accessed August 17, 2016.
24 Immune Deficiency Foundation. Characteristics of immune globulin products used to treat primary immunodeficiency diseases licensed for use in the United States. Towson, MD; Immune Deficiency Foundation; January 2016. Available at: http://primaryimmune.org/wp-content/uploads/2016/01/IDF-Ig-Product-Chart-01-20-2016.pdf. Accessed August 17, 2016.
25 Cuvitru [package insert]. Westlake Village, CA; Baxalta; September 2016.
26 Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 2006; 117:S525–553.
27 Orange JS. Clinical update in immunoglobulin therapy for primary immunodeficiency diseases. 2011; 14:1–12.Immune Deficiency Foundation. http://primaryimmune.org/wp-content/uploads/2011/04/Clinical-Update-in-Immunoglobulin-Therapy-for-Primary-Immunodeficiency-Diseases.pdf. Accessed August 17, 2016.
28 Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 2006; 117:S525–553.
29 Orange JS. Clinical update in immunoglobulin therapy for primary immunodeficiency diseases. 2011; 14:1–12.Immune Deficiency Foundation. http://primaryimmune.org/wp-content/uploads/2011/04/Clinical-Update-in-Immunoglobulin-Therapy-for-Primary-Immunodeficiency-Diseases.pdf. Accessed August 17, 2016.
30 Orange JS, Ochs HD, Cunningham-Rundles C. Prioritization of evidenced-based indications for intravenous immunoglobulin. J Clin Immunol. 2013; 33:1033–1036. doi 10.1007/s10875-013-9912-3.
31 Immune Deficiency Foundation. Characteristics of immune globulin products used to treat primary immunodeficiency diseases licensed for use in the United States. Towson, MD; Immune Deficiency Foundation; March 2013. http://primaryimmune.org/wp-content/uploads/2015/01/IDF-IVIG-Chart_rv-01-15.pdf. Accessed August 17, 2016.
32 Cuvitru [package insert]. Westlake Village, CA; Baxalta; September 2016.
33 Carimune NF [package insert]. Kankakee, IL; CSL Behring; September 2013.
34 American Academy of Allergy Asthma and Immunology. Eight guiding principles for effective use of IVIG for patients with primary immunodeficiency. 2011 December. http://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20Resources/IVIG-guiding-principles.pdf. Accessed August 17, 2016.
35 American Academy of Allergy Asthma and Immunology. Eight guiding principles for effective use of IVIG for patients with primary immunodeficiency. 2011 December. http://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20Resources/IVIG-guiding-principles.pdf. Accessed August 17, 2016.
36 Bivigam [package insert]. Boca Raton, FL; Biotest; June 2013.
37 Carimune NF [package insert]. Kankakee, IL; CSL Behring; September 2013.
38 Flebogamma 10% [package insert]. Los Angeles, CA; Grifols; January 2016.
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49 Hyqvia [package insert]. Westlake Village, CA; Baxter; April 2016.
50 Cuvitru [package insert]. Westlake Village, CA; Baxalta; September 2016.
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79 Hyqvia [package insert]. Westlake Village, CA; Baxter; April 2016.
80 Cuvitru [package insert]. Westlake Village, CA; Baxalta; September 2016.
81 FDA safety communication: new boxed warning for thrombosis related to human immune globulin products. June 10, 2013. http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm375096.htm. Accessed August 17, 2016.
82 Bivigam [package insert]. Boca Raton, FL; Biotest; June 2013.
83 Carimune NF [package insert]. Kankakee, IL; CSL Behring; September 2013.
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130 Flebogamma 5% [package insert]. Barcelona, Spain; Grifols; August 2014.
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139 Hizentra [package insert]. Kankakee, IL; CSL Behring; January 2015.
140 Hyqvia [package insert]. Westlake Village, CA; Baxter; April 2016.
141 Cuvitru [package insert]. Westlake Village, CA; Baxalta; September 2016.
142 Jolles S, Bernatowska E, de Gracia J, et al. Efficacy and safety of Hizentra in patients with primary immunodeficiency after a dose-equivalent switch from intravenous or subcutaneous replacement therapy. Clin Immunol. 2011;141(1):90-102. DOI:10.1016/j.clim.2011.06.002.
143 Borte M, Pac, M, Serban M, et al. Efficacy and safety of Hizentra, a new 20% immunoglobulin preparation for subcutaneous administration, in pediatric patients with primary immunodeficiency. J Clin Immunol. 2011;31(5):752-761. DOI: 10.1007/s10875-011-9557-z.